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## Peptide-mapping of three neutralizing epitopes into predicted biologically active sites of human interferon- $\alpha 2$

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### 1. Summary

Immunologically less reactive but functionally relevant structures were identified on human interferon (IFN)- $\alpha 2$  by three neutralizing monoclonal antibodies (mAb). The binding sites of these mAbs were mapped using a set of synthetic peptides that covered the amino acid sequence of two predicted biologically active segments in the regions 31-53 and 63-85 of IFN- $\alpha 2$ . We measured the capacity of fragments to inhibit the IFN-neutralizing activity of mAbs and located three linear epitopes around residues 42-53, 63-76 and 77-85 of the IFN- $\alpha 2$  molecule.

### 2. Introduction

Neutralizing monoclonal antibodies (mAbs) are frequently used for identifying functional domains of biologically active proteins. A structure-function study of human interferon (IFN)- $\alpha 2$  revealed two immunodominant regions associated with the amino acid residues 30-40 and 105-125 that appear to be responsible for the interaction with the IFN-cellular receptor [1-3]. The aim of the present work was the identification of other

**Key words:** Interferon- $\alpha 2$ ; Epitope-mapping; Synthetic peptide

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functionally important structures defined on the IFN- $\alpha 2$  molecule by three neutralizing mAbs. Antibodies raised against the native IFN-protein synthetic peptides can be exploited to map these functional structures. We used fragments spanning the primary sequence of two sites predicted as being biologically active of human IFN- $\alpha 2$  [4,5] and evaluated their interference with single mAbs in the IFN-neutralizing antiproliferative bioassay. Three different linear epitopes were determined on the IFN- $\alpha 2$  molecule.

### 3. Materials and Methods

#### 3.1. Monoclonal antibodies

The preparation and characterization of three murine monoclonal antibodies N8; N12 and N27 raised against human IFN- $\alpha 2c$  was described previously [1]. Hybridoma culture supernatants containing mAbs at a concentration of 0.5-1.0 µg/ml were used in the present experiments [1].

#### 3.2. Interferon

Recombinant human IFN- $\alpha 2c$  (*Escherichia coli*-derived, HPLC-purified to >98% purity, with a specific activity of  $10^8$  units per mg) was kindly provided by Prof. G. Bodo (Ernst Boehringer Institut für Arzneimittelforschung, Vienna, Austria).

### 3.3. Synthetic IFN fragments

Synthetic fragments corresponding to the conservative, highly hydrophilic regions of human IFN- $\alpha$  were used. Four oligopeptides spanning the areas of IFN- $\alpha$ 2 between residues 31–42 (KDRHDFGFPQEF), 39–53 (PQEFDQNQFQ-KAET), 63–76 (QIFNLFSTKDSSAA), and 68–85 (FSTKDSSAAWDETLLDKF) were synthesized by the solid-phase technique and purified by HPLC on a chromatograph (Gilson, France) using Zorbax C<sub>8</sub> columns (DuPont). According to the optical data at 220 nm, the concentration of the major component was found to be 99%. The peptide structure was confirmed by amino acid analysis on a D500 amino acid analyzer (Durrum).

### 3.4. Antiviral assay of IFN

The antiviral activity of IFN- $\alpha$  was determined by a cytopathic inhibition assay using Madin-Darby bovine kidney (MDBK) cells challenged with vesicular stomatitis virus in 96-well microtitre plates [1].

### 3.5. IFN-neutralizing antiproliferative assay

The inhibition of the antiproliferative activity of IFN was measured using human promyelocyte HL60 cells as indicator cells. For cultivation and IFN dilution, RPMI 1640 medium supplemented with 10% horse serum was used. The assay was performed in flat-bottom 96-well plates (Koh-i-noor, Czechoslovakia).

**Competition mAb-peptide assay:** The respective IFN- $\alpha$ 2 fragments were added in 5- $\mu$ l aliquots from a stock solution (1 mg/ml in PBS, 10<sup>-3</sup> M) to 50  $\mu$ l of hybridoma culture supernatant. The final peptide concentration in the supernatant was then 100  $\mu$ g/ml. The mAb-peptide samples were incubated for 30 min at 37°C and mixed with 50  $\mu$ l of IFN- $\alpha$ 2 (500 units/ml). Immediately thereafter 2  $\times$  10<sup>4</sup> HL60 cells in 100  $\mu$ l of cultivation medium were added to the wells. The plates were incubated for 72 h in a 6% CO<sub>2</sub> atmosphere, and the cells in the wells were counted microscopically. Each peptide-supernatant combination was plated in quadruplicate and investigated in three independent assays.

TABLE I

Peptide-mapping of IFN-neutralizing epitopes

Values given represent cell number  $\times$  10<sup>4</sup>/ml<sup>a</sup> (% of IFN-untreated homologous control).

mAb	Control	IFN + (antibody + peptide) <sup>b</sup>					
		PBS	31–42	39–53	63–76	68–85	Epitope
N8	33.9 (100)	33.2 (98)	35.5 (105)	32.5 (96)	32.2 (95)	<b>24.0</b> (71)	77–85
N12	39.1 (100)	37.9 (97)	37.1 (95)	36.4 (93)	<b>27.0</b> (69)	39.1 (100)	63–76
N27	41.1 (100)	40.3 (98)	39.5 (96)	<b>29.6</b> (72)	37.8 (92)	41.1 (100)	43–53
NSO <sup>c</sup>	38.8 (100)	27.9 (72)	27.5 (71)	26.3 (68)	28.3 (73)	27.2 (70)	

<sup>a</sup>Mean from four parallel wells. SD was less than 10% of the mean. Data from one representative experiment. Bold entries indicate significant inhibition ( $P < 0.01$ ) of mAb activity.

<sup>b</sup>5  $\mu$ l of peptide (1 mg/ml) were mixed with 50  $\mu$ l of mAb (supernatant). After 30 min, 50  $\mu$ l of IFN (500 U/ml) were added, followed by 2  $\times$  10<sup>4</sup> HL60 cells in 100  $\mu$ l.

<sup>c</sup>Supernatant of Ig-nonsecreting mouse myeloma cell line NSO.

#### 4. Results

The binding sites of three mAbs (N8, N12 and N27) which were raised against intact human IFN- $\alpha$ 2 were mapped. These antibodies neutralized both the antiviral and antiproliferative activities of IFN- $\alpha$ 2 and were directed to distinct epitopes [1]. For epitope-mapping, the oligopeptides spanning the areas of human IFN- $\alpha$ 2 between residues 31–42, 39–53, 63–67 and 68–85 were prepared. Their capacity to inhibit the neutralizing effect of mAbs was measured by the antiproliferative IFN-neutralizing assay on human HL60 cells. We found previously that this method gives reliable results with high sensitivity and precision [6,7].

The cells were cultivated in a final concentration of 125 U/ml IFN, which suppressed their growth to about 70%. This antiproliferative effect was almost totally inhibited when, before adding to the cells, the IFN was incubated for 30 min with supernatants N8, N12 and N27. The remaining IFN-neutralizing activity of test mAbs after preincubation with single peptides was determined. Table 1 shows the cell numbers, which reflect the efficacy of IFN-neutralization upon the competition of the mAb with the peptides. The residual antiproliferative activity, indicated by a significant reduction of cell number in comparison with the IFN-untreated control, reflected the inhibition (competition) of the mAb with the respective fragment. The peptides used at the final concentration (100  $\mu$ g/ml) neither had an adverse effect on cell growth (not shown) nor significantly affected the antiproliferative activity of IFN, as demonstrated with NSO-culture supernatant.

The activity of mAb N8 was inhibited by peptide 68–85 but not by peptide 63–76, suggesting that the antibody-binding site was possibly located close to the sequence 77–85. In contrast, the mAb N12 was inhibited by peptide 63–76 but not by peptide 68–85. We suppose that their epitope is formed, at least partially, by the sequence 63–67. The epitope against which the third antibody N27 was directed seemed to be located in the region 43–53, as evidenced by the blocking activity of peptide 39–53 but not peptide 31–42.

#### 5. Discussion

In our earlier study, we demonstrated two immunodominant structures on human IFN- $\alpha$ 2 around residues 30–41 and 105–125 which were involved in the biological activity of the protein [1]. Both domains were recognized by 15 of 18 mAbs tested. The three remaining antibodies, N8, N12 and N27, were used in this study to locate immunologically less reactive, but functionally relevant, sites.

These neutralizing mAbs did not inhibit the cellular binding of IFN and therefore might recognize regions that influence the conformation of the active IFN- $\alpha$  molecule. To map their binding sites, four oligopeptides covering the amino acid sequences 31–53 and 63–85 of IFN- $\alpha$ 2 were synthesized. The IFN fragments were selected according to the hypothetical antigenic map of IFN- $\alpha$ , which predicted the location of two immunologically and biologically active domains [4,5]. A bioassay based on homologous peptide blocking of mAb activity for IFN-neutralization was chosen for mapping. Using this method, we have located three linear neutralizing epitopes on human IFN- $\alpha$ 2 between residues 43–53, 63–67 and 77–85. The 'continuous' epitopes determined by peptide fragments usually represent only a portion of larger discontinuous epitopes [8]. Nevertheless, synthetic homologous peptides seem to be at least useful in the identification of specific residues or general regions recognized by an antibody [9]. The molecular localization of antigenic sites into two hydrophilic regions bound by residues 31–53 and 63–85 is consistent with the experimentally established tertiary structure of murine IFN- $\beta$  [10].

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#### References

- [1] Kontsek, P., Borecký, L., Kontseková, E., Máčiková, I., Kolcunová, A., Novák, M. and Krchňák, V. (1991) Mol. Immunol. 28, 1289.
- [2] Senda, T., Shimazu, T., Matsuda, S., Kawano, G., Shimizu, H., Nakamura, K.T. and Mitsui, Y. (1992)

- EMBO J. 11, 3193.
- [3] Fish, E.N. (1992) J. Interferon Res. 12, 257.
  - [4] Zav'yalov, V.P. and Denesyuk, A.I. (1982) Immunol. Lett. 4, 7.
  - [5] Zav'yalov, V.P., Denesyuk, A.I. and Zav'yalova, G.A. (1989) Immunol. Lett. 22, 173.
  - [6] Borecký, L., Kontsek, P., Novák, M. and Lackovič, V. (1989) Antiviral Res. 12, 195.
  - [7] Kontsek, P., Borecký, L., Kontseková, E., Kolcunová, A., Novák, M., Zav'yalov, V.P. and Maiorov, V.A. (1992) Mol. Immunol. 29, 863.
  - [8] Van Regenmortel, M.H.V. (1989) Immunol. Today 10, 266.
  - [9] Laver, W.G., Air, G.M., Webster, R.G. and Smith-Gill, S.J. (1990) Cell 61, 553.
  - [10] Senda, T., Matsuda, S., Kurihara, H., Nakamura, K.T., Kawano, G., Shimizu, H., Mizuno, H. and Mitsui, Y. (1990) Proc. Jpn. Acad. Ser. B. 66, 77.

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## **EXHIBIT C**

## BIBLIOGRAPHY

- BLOCK G et al: Fruit, vegetables, and cancer prevention: A review of the epidemiological evidence. *Nutr Cancer* 18:1, 1992
- DOLZI R, PETO R: The cause of cancer: Quantitative estimates of avoidable risks of cancer in the United States today. *J Natl Cancer Inst* 66:1191, 1981
- FLETCHER SW et al: Report of the International Workshop on Screening for Breast Cancer. *J Natl Cancer Inst* 85:1644, 1993
- GREENWALD P et al: Chemoprevention. *CA Cancer J Clin* 45:31, 1995
- et al: *Cancer Prevention and Control*. New York, Marcel Dekker, 1995
- LIPPMAN SM et al: Cancer chemoprevention. *J Clin Oncol* 12:851, 1994
- SOX HC: Preventive health services in adults. *N Engl J Med* 330:1589, 1995
- THE ALPHA-TOCOPHEROL, BETA CAROTENE CANCER PREVENTION STUDY GROUP: The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med* 330:1029, 1994
- THE COMMIT-RESEARCH GROUP: Community intervention trial for smoking cessation (COMMIT): I. Cohort results from a four-year community intervention. *Am J Public Health* 85:183, 1995
- : Community intervention trial for smoking cessation (COMMIT): II. Changes in adult cigarette smoking prevalence. *Am J Public Health* 85:193, 1995
- U.S. PREVENTIVE SERVICES TASK FORCE: *Guide to Clinical Preventive Services*, 2nd ed. Washington D.C., Government Printing Office, 1996
- WOOLF SH: Screening for prostate cancer with prostate-specific antigen. *N Engl J Med* 333:1401, 1995

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Robert G. Fenton, Dan L. Longo

## CELL BIOLOGY OF CANCER

Two characteristic features define a cancer: cell growth not regulated by external signals (i.e., autonomous) and the capacity to invade tissues and metastasize to and colonize distant sites (see Chap. 85). The first of these features, the uncontrolled growth of abnormal cells, is a property of all neoplasms, or new growths. A neoplasm may be benign or malignant. If invasion, the second cardinal feature of cancer, is present; the neoplasm is malignant. Cancer is a synonym for *malignant neoplasm*. Cancers of epithelial tissues are called *carcinomas*; cancers of nonepithelial (mesenchymal) tissues are called *sarcomas*.

Cancer is a genetic disease, but the level of its expression is the single cell. Although some forms of cancer are heritable, most mutations occur in somatic cells and are caused by intrinsic errors in DNA replication or are induced by carcinogen exposure. A single genetic lesion is usually not sufficient to induce neoplastic transformation of a cell. The malignant phenotype is acquired only after several (5 to 10) mutations (usually developing over many years) lead to rearrangements in a variety of gene products. Each genetic alteration may cause phenotypic changes typified by the progression in epithelial tissues from hyperplasia to adenoma to dysplasia to carcinoma *in situ* to invasive carcinoma. Resistance to neoplastic transformation is due to levels of control at every phase of cell function. Abnormalities in the function of one protein may be compensated by other proteins and pathways. An analogy can be drawn between the complex behavior of interacting signaling cascades and computer-based neural networks that can be adapted or trained to recognize patterns of complex inputs and respond to each pattern with a specific pattern of output.

The more than 200 discrete cell types in the body are not equally susceptible to developing cancer. Some cells, such as cardiac myocytes, sensory receptor cells for light and sound, and lens fibers, persist throughout life without dividing or being replaced. Neoplasia in such tissues is exceedingly rare. Most differentiated tissues undergo turnover characterized by cell death and replacement: When natural turnover rates are slow, fully differentiated cells may be induced to proliferate and produce fully differentiated daughter cells. For example, hepatocytes are capable of dividing to replace senescent, damaged, or surgically removed liver tissue.

In tissues with rapid turnover, such as skin, bone marrow, and gut, the differentiated function and the replacement function are carried out by different cell types. Under normal circumstances, an individual

cell is on one of two largely mutually exclusive paths: division or differentiation. Cells capable of dividing are undifferentiated (stem cells), whereas terminally differentiated cells are unable to divide. Stem cells produce daughter cells that can either become new stem cells (thus replenishing the stem cell compartment) or undergo terminal differentiation, depending on the circumstances and the environmental signals. Stem cells are distinguished from differentiating cells by different patterns of gene expression. Gene expression is the product of the tissue-specific programming of gene expression interacting with environmental factors such as cell-to-cell contact; interactions with extracellular matrix; endocrine hormones; paracrine growth and differentiation factors; and stresses such as heat, oxidation, irradiation, and physical distortion or traction.

Cancer is most common in tissues with rapid turnover, especially those exposed to environmental carcinogens and whose proliferation is regulated by hormones. The most common genetic changes involve the activation of proto-oncogenes or the inactivation of tumor suppressor genes (see Chap. 84). Although genetic damage is nearly universal in human cancer, cells with neoplastic features can be generated *in vitro* without genetic damage. Removal and *in vitro* culture of cells from the epiblast of a murine embryo lead to the uncontrolled proliferation of the cells and the generation of a teratocarcinoma cell line capable of producing tumors when inoculated into animals. The removal of these normal embryonic cells from their normal environment leads to uncontrolled growth. However, if the teratocarcinoma cells are reimplanted into an early embryo, under the inductive influence of their normal neighbors they can differentiate into normal organs and tissues appropriate for the location where they are injected.

Thus, environmental factors exert potent effects on the gene expression of target cells. The panoply of signals received by a particular cell leads to the activation of particular sets of transcription factors. The pattern of expression of transcription factors determines whether a cell will divide, differentiate, or die.

## PRINCIPLES OF CELL CYCLE REGULATION

The mechanism of cell division is substantially the same in all dividing cells and has been conserved throughout evolution. The process assures that the cell accurately duplicates its contents, especially its chromosomes. The cell cycle is divided into four phases. During M phase, the replicated chromosomes are separated and packaged into two new nuclei by mitosis and the cytoplasm is divided between the two daughter cells by cytokinesis. The other three phases of the cell cycle are called *interphase*: G<sub>1</sub> (gap 1), a period of growth during which the cell determines its readiness to commit to DNA synthesis; S (DNA synthesis), during which the genetic material is replicated and no re-replication is permitted; and G<sub>2</sub> (gap 2), during which the fidelity of DNA replication is determined and errors are corrected.

During S phase, DNA synthesis begins with the unfolding of chromatin from the DNA and the addition of DNA helicase and single-strand binding proteins that help open the double helix. Replication origins are spaced roughly 100,000 nucleotide pairs apart throughout the genome. DNA polymerase and DNA primase attach to these sites and catalyze the polymerization of the DNA at a rate of about 50 nucleotides per second. Topoisomerases break and reseal DNA strands to prevent tangling. Although this system for replication is efficient and accurate, occasional mistakes are made, and these mistakes in the replicated sequences are repaired by a variety of mechanisms. In some cancers, the mismatch repair mechanisms are defective and errors are routinely passed along to daughter cells, increasing the development of new mutations. Once a DNA segment is replicated and the replication units reassembled, chromatin binds to the nascent DNA chain, assuring that each region is replicated only once. DNA polymerase is unable to replicate the end of a DNA chain completely. This problem has been solved by the addition of tandem repeats of a six-nucleotide sequence (GGGTAA) to the ends of each chromosome. These repeated



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